REMARKS

Applicant has amended claim 8 to recite that the Protein C or Activated Protein C polypeptide includes a GLA domain, the GLA domain having at least one amino acid substitution at residues 2, 5, 9, 11, 12, 29, 33, 34, 35 or 36, wherein the at least one amino acid substitution enhances membrane binding affinity and activity of the polypeptide relative to a protein C or activated protein C polypeptide having the Gla domain of SEQ ID NO:1, wherein the GLA domain includes at least 35 unsubstituted residues, and wherein all of the unsubstituted residues correspond to the amino acid sequence of SEQ ID NO:1. Support for this amendment can be found throughout the specification, including at page 9, lines 9-10 and 18-19, and page 11, lines 9-20.

Claim 12 was amended to correct a typographical error.

New independent claim 61 recites that the Protein C or Activated Protein C polypeptide comprises a GLA domain defined with reference to SEQ ID NO:1, but having one to ten amino acid substitutions at a position or positions selected from the group consisting of 2, 5, 9, 11, 12, 29, 33, 34, 35 and 36, provided that if position 33 is substituted with γ-carboxyglutamic acid, at least one additional substitution is made at position 2, 5, 9, 11, 12, 29, 34, 35, or 36. New dependent claims 62-66 depend directly or indirectly from claim 61. Claim 62 recites that the protein C or activated protein C polypeptide is an active-site modified activated protein C polypeptide. Claims 63-66 relate to a pharmaceutical composition containing the protein C or activated protein C polypeptide of claim 61 or methods of using the protein C or activated protein C polypeptide of claim 61. Support for these claims can be found throughout the specification, including at page 9, lines 9-10 and lines 18-19, page 11, lines 9-32, page 18, lines 18-28, and page 20, line 27 through page 21, line 3.

New independent claim 67 recites that the Protein C or Activated Protein C polypeptide comprises a GLA domain defined with reference to SEQ ID NO:1, but having one to ten amino acid substitutions at a position or positions selected from the group consisting of 2, 5, 9, 11, 12, 29, 33, 34, 35 and 36, provided that if position 33 is substituted, at least one additional substitution is made at position 2, 5, 9, 11, 12, 29, 34, 35, or 36. New dependent claims 68-72 depend directly or indirectly from claim 67. Claim 68 recites that the protein C or activated protein C polypeptide is an active-site modified activated protein C polypeptide. Claims 69-72

relate to a pharmaceutical composition containing the protein C or activated protein C polypeptide of claim 67 or methods of using the protein C or activated protein C polypeptide of claim 67. Support for these claims can be found throughout the specification, including at page 9, lines 9-10 and lines 18-19, page 11, lines 9-32, page 18, lines 18-28, and page 20, line 27 through page 21, line 3.

New independent claim 73 recites a Protein C or Activated Protein C polypeptide comprising a GLA domain having at least one amino acid substitution at residues selected from the group consisting of residues 11, 12, 33 and 34, and at least one additional amino acid substitution at residues selected from the group consisting of residues 2, 5, 9, 11, 12, 29, 33, 34, 35 and 36, wherein the amino acid substitutions enhance membrane binding affinity of the polypeptide relative to a protein C or activated protein C polypeptide having the Gla domain of SEQ ID NO:1, wherein the GLA domain comprises at least 35 unsubstituted residues, and wherein all of the unsubstituted residues correspond to the amino acid sequence of SEQ ID NO:1.

New independent claim 74 recites a Protein C or Activated Protein C polypeptide comprising a GLA domain having at least one amino acid substitution at residues selected from the group consisting of residues 11, 12, 33 and 34, and at least one additional amino acid substitution at residues selected from the group consisting of residues 2, 5, 9, 11, 12, 29, 33, 34, 35 and 36, wherein the amino acid substitutions enhance membrane binding affinity of said polypeptide relative to a protein C or activated protein C polypeptide having the Gla domain of SEQ ID NO:1, wherein the GLA domain has no more than 10 substituted residues, wherein all unsubstituted residues of said Gla domain correspond to the amino acid sequence of SEQ ID NO:1. Dependent claim 75 recites that the amino acid substitutions enhance activity of the polypeptide relative to a protein C or activated protein C polypeptide having the Gla domain of SEQ ID NO:1. Support for new claims 73-75 can be found throughout the specification, including, for example, at page 3, lines 18-26, page 9, lines 9-20, and page 11, lines 9-20.

Applicant respectfully requested reconsideration and allowance of claims 8-14 and 61-75 in view of the above amendments and following remarks.

Correspondence Address

The Office Action was mailed in error to Eli Lilly and Company. Applicant notes that all correspondence should be addressed to Fish & Richardson as set out in the transmittal letter filed with the patent application on February 5, 2000, and in the Combined Declaration and Power of Attorney filed on May 8, 2000.

Objections

The Examiner objected to claims 8-14 for depending from non-elected claim 1. Amended claim 8 is an independent claim.

The Examiner objected to claim 12 for a typographical error in line 2. Applicant has amended claim 12 to recite "further comprises a glutamic acid."

The Examiner is requested to withdraw the objections to claims 8-14.

Drawings

The drawings were objected to for reasons cited in the Form PTO-948. Formal drawings are being submitted to the Official Draftsperson under separate cover.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 9-14 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserted that there was "no reference point for the amino acid position at which the substitution is made." Applicant notes that in the Response to Restriction Requirement mailed on August 27, 2001, claims 9-14 were amended to include a reference point. For example, claim 9 was amended as follows: The polypeptide of claim 8, wherein said amino acid substitution comprises a glycine residue at amino acid 12 (corresponding to amino acid position 11 of SEQ ID NO:1). Similar amendments were made for claims 10-14. Thus, Applicant submits that the claims include a reference point.

The Examiner asserted that claims 8-14 were indefinite for the recitation of "corresponding native vitamin K-dependent polypeptide" in claim 1. The Examiner suggested amending the claim to recite "relative to a protein C polypeptide having a Gla domain of SEQ ID NO:__." Applicant has amended claim 8 as suggested by the Examiner. In view of the above,

the Examiner is requested to withdraw the rejection of claims 8-14 under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claim 8 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserted that the specification "does not reasonably provide enablement for any protein C or APC from any source (human or bovine for example) comprising a GLA domain with any number of substitutions or any positions substituted that has the claimed activity."

The specification enables one of ordinary skill in the art to make and use the claimed protein C or activated protein C polypeptides. The nucleotide and amino acid sequences of the entire human protein C polypeptide was known at the time of filing. The specification provides the GenBank Accession number as well as a reference for wild type protein C. See, the specification at page 31, lines 28-30. Furthermore, the wild-type amino acid sequence for the human protein C Gla domain (SEQ ID NO: 1) is provided at page 11, line 5 of the specification.

Applicant submits that the specification provides a number of examples of amino acid residues that can be substituted within the Gla domain of protein C. The specification indicates that conservative amino acid substitutions that replace an amino acid with an amino acid residue of the same class can be made in the Gla domain. See, specification at page 9, lines 11-13. Non-conservative substitutions, which include replacing an amino acid with an amino acid of a different class, also can be made in the Gla domain. See, specification at page 9, line 11-13. The specification provides examples of non-conservative amino acid substitutions, including substitutions of basic amino acids for non-polar amino acids, or polar amino acids for acidic amino acids. See specification at page 9, lines 13-18. In addition, the specification indicates that a glycine residue can be substituted at amino acid 12, a glutamic acid residue can be substituted at amino acid 33, and an aspartic acid or glutamic acid residue can be substituted at amino acid 34. The specification also indicates that a glutamine can be substituted at amino acid 11, a phenylalanine can be substituted at amino acid 29, and that a glutamic acid or aspartic acid residue can be substituted at amino acid 35. See, specification at page 11, lines 10-20.

The specification also describes how to make polypeptides of the invention. For example, pages 42-43 of the specification describe the production of protein C with enhanced membrane binding affinity and activity using a polymerase chain reaction (PCR) strategy. PCR primers are denoted by nucleotide location. See, for example, page 32, lines 1-6. Nucleic acid fragments were generated with this strategy, and ligated to produce a nucleic acid encoding a full-length protein C polypeptide. Detailed methods also are provided for the purification of protein C. See, for example, page 33, line 12 through page 34, line 29.

Furthermore, the specification describes techniques for determining membrane affinity of protein C polypeptides. In general, vesicles of phosphatidylserine and phosphatidylcholine can be prepared, and protein can be added at different weight ratios. Protein-membrane binding then can be assayed by a light scattering technique. See, specification, page 10, lines 18-21. Activity of protein C can be assessed using the APTT assay. See, specification at page 36, lines 13-17.

Thus, the specification provides examples of particular amino acid substitutions that can be made within the Gla domain and provides a test to determine if particular amino acid substitutions enhance membrane binding and activity of the polypeptide. As such, the specification enables one of ordinary skill in the art to make and use the claimed protein C or activated protein C polypeptides. The Examiner is requested to withdraw the rejection of claim 8 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 8, 9 and 10 under 35 U.S.C. § 102(b) as being anticipated by Hashimoto et al. (EP 0 354 504); claims 8, 9 and 14 under 35 U.S.C. § 102(b) as being anticipated by Wakako et al. (EP 0 296 413); and claims 8, 9 and 14 under 35 U.S.C. § 102(e) as being anticipated by Smirnov et al. (U.S. Patent No. 5,837,853). The Examiner asserted that "Hashimoto et al. teach a protein C hybrid polypeptide wherein the Gla domain has been substituted with the Gla domain of Factor X (FX)." The Examiner characterized the Wakako et al. reference as teaching "a human protein C hybrid polypeptide wherein the Gla domain has been substituted with the Gla domain of bovine protein C" and alleged that the protein of Wakako et al. would inherently have the same activity as the claimed protein. The Examiner asserted that Smirnov et al. "teach a protein C chimeric polypeptide wherein the Gla domain has

been substituted with the Gla domain of prothrombin" and that the protein C polypeptides of Smirnov et al. "are structurally identical and patentably indistinguishable from those of present claims 8, 9, and 14."

Each of the cited references discloses chimeric protein C polypeptides where the Gla domain of human protein C was replaced with the Gla domain from a different species or from a different vitamin K-dependent protein. The cited references do not disclose the protein C or activated protein C polypeptides of claims 8, 9, 10, and 14. Amended independent claim 8 recites that the GLA domain has at least one amino acid substitution at residues 2, 5, 9, 11, 12, 29, 33, 34, 35 or 36 that enhances membrane binding affinity and activity of the polypeptide and that the GLA domain includes at least 35 unsubstituted residues, wherein all of the unsubstituted residues correspond to the amino acid sequence of SEQ ID NO:1. Thus, the cited references do not anticipate the presently claimed invention. The Examiner is requested to withdraw the rejections under 35 U.S.C. §102(b) and §102(e).

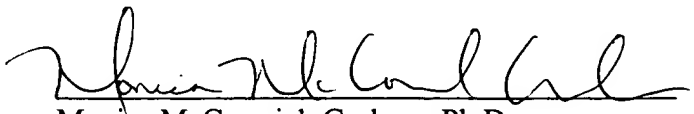
CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that claims 8-14 and 61-75 be allowed. Enclosed is a petition for a three-month extension of time with the check for the extension of time fees. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 5/20/02



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Version with markings to show changes made

In the claims:

Claims 1-7 and 15-60 have been cancelled.

Claims 8 and 12 have been amended as follows:

8. (Amended) [The polypeptide of claim 1, wherein said polypeptide comprises] A Protein C or Activated Protein C polypeptide comprising a GLA domain, said GLA domain having at least one amino acid substitution at residues 2, 5, 9, 11, 12, 29, 33, 34, 35 or 36 wherein said at least one amino acid substitution enhances membrane binding affinity and activity of said polypeptide relative to a protein C or activated protein C polypeptide having the Gla domain of SEQ ID NO:1, wherein said GLA domain comprises at least 35 unsubstituted residues, and wherein all of said unsubstituted residues correspond to the amino acid sequence of SEQ ID NO:1.

12. (Twice Amended) The polypeptide of claim 11, wherein said at least one amino acid substitution further comprises [or] a glutamic acid residue at amino acid 36 (corresponding to amino acid position 35 of SEQ ID NO:1).